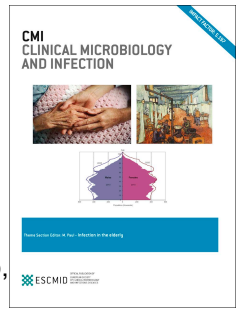
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal Pre-proof



Inappropriate use of ivermectin during the COVID-19 pandemic: Primum non nocere!

Aleksandra Barac, Michele Bartoletti, Ozlem Azap, Linda Bussini, Onder Ergonul, Robert Krause, José Ramón Paño-Pardo, Nicholas R. Power, Jesús Rodríguez-Baño, Marcella Sibani, Balint Gergely Szabo, Sotirios Tsiodras, Paul E. Verweij, Alejandro Martín Quirós, Ines Zollner-Schwetz

PII: S1198-743X(22)00161-6

DOI: https://doi.org/10.1016/j.cmi.2022.03.022

Reference: CMI 2894

To appear in: *Clinical Microbiology and Infection*

Received Date: 18 December 2021

Revised Date: 14 March 2022

Accepted Date: 15 March 2022

Please cite this article as: Barac A, Bartoletti M, Azap O, Bussini L, Ergonul O, Krause R, Paño-Pardo JR, Power NR, Rodríguez-Baño J, Sibani M, Szabo BG, Tsiodras S, Verweij PE, Quirós AM, Zollner-Schwetz I, Inappropriate use of ivermectin during the COVID-19 pandemic: Primum non nocere!, *Clinical Microbiology and Infection*, https://doi.org/10.1016/j.cmi.2022.03.022.

Commentary

Inappropriate use of ivermectin during the COVID-19 pandemic: Primum non nocere!

Aleksandra Barac[1], Michele Bartoletti[2], Ozlem Azap[3], Linda Bussini[4], Onder Ergonul[5], Robert Krause[6], José Ramón Paño-Pardo[7], Nicholas R. Power[8], Jesús Rodríguez-Baño[9], Marcella Sibani[10], Balint Gergely Szabo[11], Sotirios Tsiodras[12], Paul E. Verweij[13], Alejandro Martín Quirós[14], Ines Zollner-Schwetz[6]

Affiliations:

1 Clinic for Infectious and Tropical Diseases, Clinical Center of Serbia, Belgrade, Serbia; Faculty of Medicine, University of Belgrade, Belgrade, Serbia

2 Infectious Diseases Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Policlinico di Sant'Orsola, Bologna, Italy; Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Bologna, Italy

3 Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Başkent University, Ankara, Turkey

4 Infectious Diseases Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Policlinico di Sant'Orsola, Bologna, Italy

5 Koc University Research Center for Infectious Diseases, Istanbul, Turkey

6 Division of Infectious Diseases, Department of Internal Medicine, Medical University of Graz, Graz, Austria

7 Fundación Instituto de Investigación Sanitaria Aragón (IIS Aragón), Biomedical Research Centre of Aragón (CIBA), Zaragoza, Spain; Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain

8 Royal College of Physicians of Ireland, Setanta House, Setanta Pl, Dublin, Ireland

9 Clinical Unit of Infectious Diseases and Microbiology Virgen Macarena University Hospital and Department of Medicine, University of Seville, Institute of Biomedicine of Seville, Seville, Spain

10 Infectious Diseases Section, Department of Diagnostics and Public Health, University of Verona, Verona, Italy

11 South Pest Central Hospital, National Institute of Hematology and Infectious Diseases, Budapest, Hungary; Semmelweis University, School of PhD Studies, Budapest, Hungary

12 Fourth Department of Internal Medicine, Medical School, National and Kapodistrian University of Athens, Attikon University Hospital, Athens, Greece.

13 Department of Medical Microbiology and Radboudumc-CWZ Center of Expertise for Mycology, Radboud University Medical Center, Nijmegen, The Netherlands

14Emergency Department and Emergent Pathology Research Group, IdiPAZ La Paz University Hospital, Madrid, Spain

Running title: Ivermectin and COVID-19

Key words: Ivermectin, COVID-19, treatment, ESCMID guidelines, clinical trial

Corresponding:

Aleksandra Barac, MD, PhD, Scientific Associate

Clinic for Infectious and Tropical Diseases, Clinical Center of Serbia, Belgrade, Serbia; Faculty of Medicine, University of Belgrade, Belgrade, Serbia

Conflict of interest: None.

Commentary

There is an ongoing debate worldwide about the possible benefits of ivermectin for the treatment and prevention of COVID-19. Some advocacy groups concluded, based on limited, early studies, that ivermectin might be beneficial. They continuously lobby for the widespread use of ivermectin for the treatment and prevention of COVID-19, especially through social media. Based on their advice, some medical doctors of different specialties in many countries have recommended the use of ivermectin for COVID-19 treatment and prevention. On the contrary, official bodies such as the World Health Organization (WHO), the European Medicines Agency (EMA) and Food and Drug Administration (FDA) currently assert that available evidence does not support the use ivermectin for the treatment or prevention of COVID-19 outside of well-designed randomized studies [1].

Ivermectin is derivative of avermectins family of macrocyclic lactones that exhibits broad-spectrum anti-parasitic activity. It is authorized for the treatment of for onchocerciasis and strongyloidiasis in humans, as well as for veterinary use for a large range of animal species for internal and external parasites, and it has been approved by FDA for these purposes [2]. In addition, several topical ivermectin formulations are permitted for the treatment of external parasites like head lice, as well as skin disorders including acarodermatitis and rosacea.

Ivermectin has shown *in vitro* activity against SARS-CoV-2, however, it is very important to mention that this *in vitro* activity occurred at much higher concentrations than those achieved in human plasma and lung tissue for usual doses [3]. In animal models, ivermectin has been found to have anti-inflammatory effects and hence, it was hypothesized that this additional anti-inflammatory mechanism may also have some effects in the treatment of COVID-19 [4]. Although evidence was lacking that ivermectin concentrations achieved in *in vitro* SARS-CoV2

research can be replicated in humans [2], these studies have been used as a basis to start the process of repurposing of this old drug for a novel infection.

One of the first preprint papers that supported the idea ivermectin could be successful in a clinical-trial setting, was the study led by Elgazzar and colleagues. However, on 14 July 2021, after members of the scientific community raised serious concerns about plagiarism, patient cloning and data manipulation, the preprint server Research Square withdrew the paper because of ethical concerns. Numerous other studies on ivermectin's role in treatment and prevention of COVID-19 have been published. However, the majority of the studies were observational, and it appears that some "controlled" experiments used convenience samples. The number of patients included was very small in most studies and there was substantial variation in dose. There are several concerns about these studies that strongly limit the conclusions that can be drawn from the data presented. For example, it is impossible to adjust for indication bias in observational studies without an appropriate sample size. Two meta-analyses included many of these case series, observational or open-label studies [5, 6]. However, a meta-analysis cannot correct for bias in the primary studies.

The most stringent analysis was published by Popp et al. as a Cochrane database systematic review published in July 2021. Only randomized controlled trials (RCTs) comparing ivermectin to no therapy, standard of care, placebo, or another established intervention for COVID-19 treatment were included in this analysis. Fourteen RCTs on the treatment and prevention of COVID-19 in different settings were included in this meta-analysis. However, not all trials addressed the same specific outcomes e.g. clinical worsening or need for supplemental oxygen. Therefore, the number of participants per outcome is often very small. The authors assessed RCTs for bias, using the Cochrane risk of bias 2 tool. They found very low- to low-certainty evidence for all outcomes [7]. For inpatients as well as outpatients, there was no significant difference between the groups in terms of all-cause mortality and clinical worsening [7].

Overall, the conclusion was that "reliable evidence available does not support the use ivermectin for treatment or prevention of COVID-19 outside of well-designed randomized trials" [7].

The publications on the possible effects of ivermectin on the treatment and prevention of COVID-19 highlight some of the negative effects of the pandemic on scientific work. Many single-center, observational studies were launched looking into research questions that they could not answer appropriately. Resources such as money, researchers' time and effort were used in redundant studies as has been discussed before [8]. The pandemic also underlined the need for international networks and trial platforms such as the WHO led Solidarity trial that are able to start recruiting patients quickly if the need arises.

Adhering to recommended doses, ivermectin is generally well tolerated. Common side effects associated with ivermectin include diarrhea and nausea. However, significant symptoms can arise when ivermectin is overdosed. Symptoms of ivermectin overdose include gastrointestinal symptoms such as nausea, vomiting, and diarrhea [9]. In addition, hypotension and neurologic effects such as decreased consciousness, confusion, hallucinations, seizures, coma, and death have been described [9]. Hospitalizations due to inappropriate ivermectin use and subsequent severe side effects have been noted in several European countries (personal communication). In comparison to the prepandemic baseline, calls to poison control centers due to ivermectin intake have increased 5-fold in the United States as reported by CDC [10]. Ivermectin may also magnify the effects of other substances that cause central nervous system depression, such as benzodiazepines, and it can interact with other medications, such as anticoagulants, even at levels approved for human anti-parasitic usage. Furthermore, providing patients a false feeling of security might cause indirect harm, especially if they choose ivermectin instead of seeking hospital treatment for COVID-19 or being vaccinated in the first place.

All guideline committees assessed the overall certainty of evidence for the use of ivermectin in the treatment and prevention of COVID-19 as low or very low after considering all of these factors [1, 2, 10]. The ESCMID COVID guidelines committee on drug treatment and clinical management agreed on a strong recommendation against any use of ivermectin to treat COVID-19 patients [10].

Misinformation on potential COVID-19 remedies disseminated by unofficial sources is widespread in many countries, which could lead to inappropriate and even dangerous use of this drug that is increasingly sold via illegitimate online pharmaceutical markets. Furthermore, the rise of false information in social media but also scientific literature continues to fuel vaccination hesitancy, mistrust in health authorities, anxiety, and the use of untested COVID-19 preventative and treatment measures, which is alarming. It is understandable that an inexpensive and widely available treatment for COVID-19 is desperately wanted all over the world. This is especially true for health-care systems dealing with low vaccination rates. Even in a pandemic crisis, however, it is unethical and immoral to advocate for the broad use of a medication that has not been proven effective in clinical trials. Prescribing a substance just because it has not been shown ineffective, goes against medicine's guiding principle of 'first, do no harm'. We should not ignore this principle, especially given the large amount of ongoing research into the benefit and harm of ivermectin as treatment or prevention of COVID-19, which is still being carried out in this pandemic. The results from the available well-designed clinical studies so far do not support the commonly promoted benefits of ivermectin. The risk of injury by ivermectin is not balanced by any benefits of this drug in the treatment and prevention of COVID-19. Ivermectin has been shown to have negative side effects when used to prevent or treat COVID-19. As a result, ivermectin should not be used to treat COVID-19.

Transparency declaration:

Conflict of interest disclosure: Authors have no any conflict of interest.

Study has no funding.

None external funding has been received for this manuscript.

References

[1] https://www.ema.europa.eu/en/news/ema-advises-against-use-ivermectin-prevention-treatment-covid-19-outside-randomised-clinical-trials. Accessed on December 4, 2021

[2] Drugs.com. Ivermectin tablets. FDA professional drug information. https://www.drugs.com/pro/ivermectin-tablets.html. Updated February 21, 2021. Accessed on December 4, 2021

[3] Bray M, Rayner C, Noel F, Jans D, Wagstaff K. Ivermectin and COVID-19: A report in Antiviral Research, widespread interest, an FDA warning, two letters to the editor and the authors' responses. Antiviral Res 2020; 178: 104805. doi: 10.1016/j.antiviral.2020.104805.

[4] Yan S, Ci X, Chen N, et al. Anti-inflammatory effects of ivermectin in mouse model of allergic asthma. Inflamm Res 2011; 60(6): 589-96. doi: 10.1007/s00011-011-0307-8.

[5] Kory P, Meduri GU, Varon J, Iglesias J, Marik PE. Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19. Am J Ther. 2021; 28(3):e299-e318. doi: 10.1097/MJT.0000000000001377.

[6] Bryant A, Lawrie TA, Dowswell T, Fordham EJ, Mitchell S, Hill SR, Tham TC. Ivermectin for Prevention and Treatment of COVID-19 Infection: A Systematic Review, Meta-analysis, and Trial Sequential Analysis to Inform Clinical Guidelines. Am J Ther. 2021; 28(4):e434-e460. doi: 10.1097/MJT.0000000000001402.

[7] Popp M, Stegemann M, Metzendorf MI, Gould S, Kranke P, Meybohm P, Skoetz N, Weibel S. Ivermectin for preventing and treating COVID-19. Cochrane Database Syst Rev. 2021; 7(7):CD015017. doi: 10.1002/14651858.CD015017.pub2.

[8] Paul M, Kalil AC. Repurposed drugs for COVID-19: threshold and proof requirements for trials. Clin Microbiol Infect. 2021; 27(12):1716-1717. doi: 10.1016/j.cmi.2021.08.024.

[9] CDC Health Alert Network. Rapid increase in ivermectin prescriptions and reports of severe illness associated with use of products containing ivermectin to prevent or treat COVID-19.https://emergency.cdc.gov/han/2021/pdf/CDC_HAN_449.pdf. Accessed on December 4, 2021

[10] Bartoletti M, Azap O, Barac A, Bussini L, Ergonul O, Krause R, Paño-Pardo JR, et al. ESCMID COVID-19 Living guidelines: drug treatment and clinical management. Clin Microbiol Infect. 2021: S1198-743X(21)00634-0. doi: 10.1016/j.cmi.2021.11.007.

Author's contributions:

AB and IZS conceptualized the paper and wrote the first draft. MB, OA, LB, OE, RK, JRPP, NP, JRB, MS, BGS, ST, PV and AMQ performed the literature search. All authors contributed to the manuscript writing. All authors listed have made a substantial, direct and intellectual contribution to the work, and approved final version of the manuscript for submission.